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Structural effect in the reductive vinylation/phosphorylation of pyridines with alkyl propiolates and secondary phosphine chalcogenides: protonation *vs*. zwitterion generation

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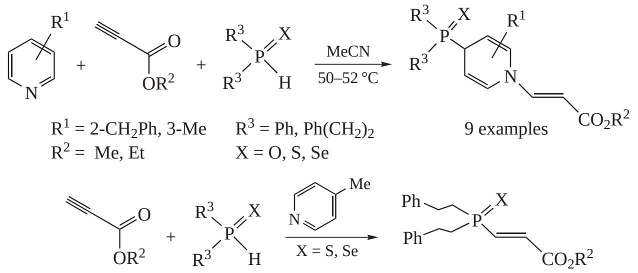
The non-catalyzed reaction of 2- and 3-substituted pyridines with alkyl propiolates and secondary phosphine chalcogenides (50–52 °C, MeCN) produces stereo-, regio- and chemoselectively 1-[(*E*)-2-(alkoxycarbonyl)ethenyl]-4-chalcogenophosphoryl-1,4-dihydropyridines in 57–90% yields, the adducts of pyridines with alkyl propiolates being the zwitterionic intermediates. 4-Methylpyridine mainly catalyzes nucleophilic addition of secondary phosphine chalcogenides to alkyl propiolates.



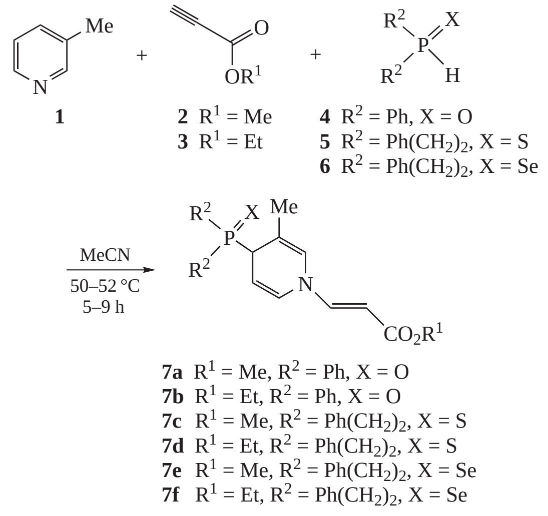
Multicomponent reactions, allowing complex heterocyclic molecules to be constructed in a one preparative step, are now intensively developed.[1] Recently, we have found that pyridine and its 2-methyl derivative, when treated with alkyl propiolates and secondary phosphine chalcogenides (20–52 °C, 3–8 h, MeCN), undergo stereo-, regio- and chemoselective vinylation/phosphorylation to afford the corresponding 1-(*E*)-ethenyl-4-chalcogenophosphoryl-1,4-dihydropyridines.[2] However, under the same conditions quinoline experiences the attack by the chalcogenophosphoryl moieties at the 2-position to give the corresponding 1-(*E*)-ethenyl-2-chalcogenophosphoryl-1,2-dihydroquinolines, thus demonstrating another regio direction of this three-component process and its high sensitivity towards the structural effects.[3] In the above reactions, the formation of possible adducts of secondary phosphine chalcogenides with alkyl propiolates was not observed.[2,3]

To better rationalize the regio- and chemoselectivity of this synthetically[4] and pharmaceutically[5] promising reaction, here we have studied how the methylation pattern in pyridine influences the outcome of the process. It is common that introduction of substituents into the pyridine ring is often crucial for its reactivity.[6]

As our experiments have shown, 3-methylpyridine **1**, when reacted with alkyl propiolates **2**, **3** and secondary phosphine chalcogenides **4**–**6** (50–52 °C, 5–9 h, MeCN, without catalyst), follows the same route as the reaction with pyridine and its 2-methyl derivative,[2] *i.e*. undergoing 1,4-difunctionalization of the pyridine ring to deliver 1-[(*E*)-2-(alkoxycarbonyl)ethenyl]-4-chalcogenophosphoryl-1,4-dihydropyridines **7a**–**f** in 62–90% yields (Scheme 1).†

Under these conditions (50–52 °C, MeCN), 2-benzylpyridine **8** turns out to be the least reactive giving products **9a**–**c** within 16–20 h (*vs*. 5–9 h in the case of pyridine **1**) in 57–65% yields (Scheme 2).†

Apparently, a bulky substituent in pyridine **8** (compared with 2- and 3-methylpyridines) creates steric hindrances for the formation of zwitterions **A** and **C** generated from pyridines and propiolates at the first stage of the process (Scheme 3), whose tentative mechanism was discussed earlier.[2]



1

2 R^1 = Me
3 R^1 = Et

4 R^2 = Ph, X = O
5 R^2 = Ph(CH_2)$_2$, X = S
6 R^2 = Ph(CH_2)$_2$, X = Se

7a R^1 = Me, R^2 = Ph, X = O
7b R^1 = Et, R^2 = Ph, X = O
7c R^1 = Me, R^2 = Ph(CH_2)$_2$, X = S
7d R^1 = Et, R^2 = Ph(CH_2)$_2$, X = S
7e R^1 = Me, R^2 = Ph(CH_2)$_2$, X = Se
7f R^1 = Et, R^2 = Ph(CH_2)$_2$, X = Se

Scheme 1

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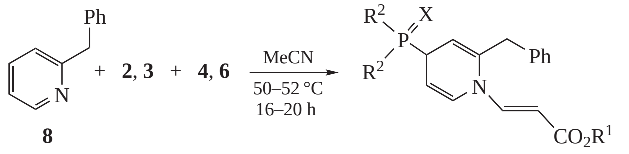
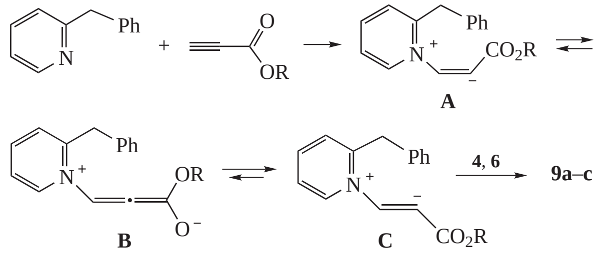
† *1-[(*E*)-2-(alkoxycarbonyl)ethenyl]-4-chalcogenophosphoryl-1,4-dihydropyridines* **7a**–**f**, **9a**–**c** *(general procedure)*. A solution of methyl pyridine **1**, **8** (1.1 mmol), alkyl propiolate **2**, **3** (1.1 mmol) and secondary phosphine chalcogenide **4**–**6** (1.0 mmol) in MeCN (3 ml) was stirred under an argon atmosphere at 50–52 °C for 5–9 h (for compounds **7a**–**f**) or 16–20 h (for compounds **9a**–**c**). After completion of the reaction (^{31}P NMR monitoring), the solvent was removed under reduced pressure and the residue was purified by flash chromatography (for compounds **7a**,**b**, **9a**: SiO_2, benzene–1,4-dioxane, 7 : 1; for compounds **7c**–**f**, **9b**,**c**: Al_2O_3, hexane–acetone–chloroform, 14 : 2 : 1).



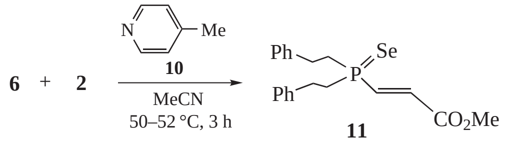
9a R^1 = Me, R^2 = Ph, X = O
9b R^1 = Me, R^2 = $Ph(CH_2)_2$, X = Se
9c R^1 = Et, R^2 = $Ph(CH_2)_2$, X = Se

Scheme 2



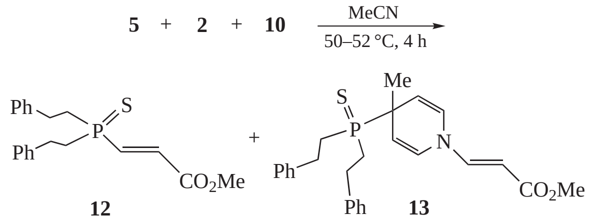
Scheme 3

Surprisingly, 4-methylpyridine **10**, when allowed to contact with acetylene **2** and secondary phosphine selenide **6**, did not undergo the vinylation/phosphorylation sequence. Instead, the Michael adduct **11** of propiolate **2** with phosphine selenide **6** was exclusively formed in 75% yield (Scheme 4).‡



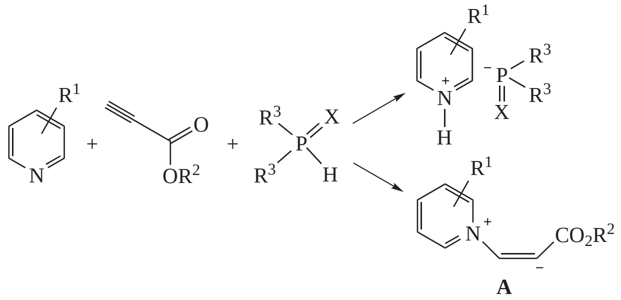
Scheme 4

The same reaction with phosphine sulfide **5** leads to the mixture of the Michael adduct **12** and 1,4-dihydropyridine **13** (in a ~1.4 : 1 ratio, ^{31}P NMR), which were separated in 34 and 25% yields, respectively (Scheme 5).‡



Scheme 5

To rationalize these results, the two competitive initial reactions should be considered: protonation of pyridines with secondary phosphine chalcogenides and nucleophilic addition of pyridines to the triple bond of alkyl propiolates to give zwitterions (Scheme 6).



Scheme 6

Apparently, 4-methylpyridine, being more basic compared with 2- and 3-methyl derivatives (pK_a = 6.05, 5.96, 5.68, respectively),[7] is preferably protonated by the most acidic secondary phosphine selenide **6** (compared with other phosphine chalcogenides[8]) instead of generation of zwitterions and therefore the nucleophilic addition of selenophosphinite anion to propiolate **2** predominates. 4-Methylpyridine, in this case, plays a role of basic catalyst.

As the acidity of secondary phosphine chalcogenides decreases going from sulfides to oxides,[8] the zwitterion generation becomes competitive and with oxide **4** completely wins. However, due to the weaker acidity of secondary phosphine oxide,[8] zwitterion **A** is not quenched with proton (the phosphine oxide remaining intact) but adds the second molecule of methyl propiolate to give finely the Acheson adduct.[9]

In conclusion, for the non-catalyzed reaction between substituted pyridines, alkyl propiolates and secondary phosphine chalcogenides, the structural effects controlling the competition between the three-component reductive vinylation/phosphorylation of the pyridine ring and the normal nucleophilic addition of secondary phosphine chalcogenides to alkyl propiolates have been established and analyzed. In view of the common knowledge that dihydropyridines are key structural motifs in antihypertensive pharmaceuticals (amlodipine, nifedipine, felodipine) and biologically active compounds with anticonvulsant,[5(*a*)] anticoagulant,[5(*b*)] antitumor,[5(*c*)] antitubercular[5(*d*)] properties, the developed atom-economic, one-pot, high yield approach closed to the PASE[10] requirements may become available contribution to the drug design.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.11.004.

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‡ *4-Methylpyridine* **10** *in the reaction of phosphine chalcogenides* **5** *or* **6** *with methyl propiolate* **2**. A solution of 4-methylpyridine **10** (1.65 mmol), methyl propiolate **2** (1.65 mmol) and phosphine chalcogenide **5**, **6** (1.5 mmol) in MeCN (4.5 ml) was stirred under an argon atmosphere at 50–52 °C for 4 h in case of phosphine sulfide **5** and for 3 h in case of phosphine selenide **6**. After completion of the reaction (^{31}P NMR monitoring), the solvent was removed under reduced pressure and the residue was purified by flash chromatography for monoadduct **11** on Al_2O_3 (hexane–acetone–chloroform, 14 : 2 : 1). Compounds **12** and **13** were isolated on silica gel using benzene–Et_2O (7 : 1) as an eluent.

For detailed experimental procedures and characteristics of compounds **7a**–**f**, **9a**–**c** and **11**–**13**, see Online Supplementary Materials.

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